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Cadmium: Exposure Markers as Predictors of Nephrotoxic Effects

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Cadmium (Cd) is a cumulative element with a biological half-life of >10 years in humans. The total amount of Cd accumulated in the liver and in the kidney can be measured *in vivo* by neutron activation (or x-ray fluorescence), but this technique does not necessarily measure the fraction that is biologically active. At low exposure (i.e., general environmental exposure or moderate occupational exposure), blood Cd is mainly influenced by the last 2 to 3 months of exposure. Under such conditions, the Cd concentration in urine mainly reflects the amount of Cd stored in the body, particularly in the kidney. In Europe and the US, the Cd reference values are usually <2 nmol/mmol creatinine. Because most of the Cd in urine is probably bound to metallothionein, the changes in the urinary metallothionein concentration parallel those of Cd. The determination of Cd concentration in hair is of limited value because in humans it is difficult to distinguish between externally deposited and endogenous Cd. Fecal Cd is a good indicator of the oral daily intake. The results of several cross-sectional epidemiologic studies of the relation between the prevalence of renal dysfunction and Cd concentration in urine led us to propose a biological limit value for Cd of 5 and 2 nmol/mmol creatinine for adult male workers and the general population, respectively.

Indexing Terms: metabolism/biological monitoring/renal markers/toxicology

The metabolism of cadmium (Cd) has been reviewed recently (1). Exposure of the nonsmoking general population to Cd is mainly through food, whereas for smokers tobacco is also an important source of Cd exposure. In the occupational setting, inhalation of Cd-containing dust and fumes is the major route of uptake. The oral absorption rate is in the 2-7% range, with values of up to 20% for subjects with very low iron stores. A pulmonary absorption rate of 25-50% has been estimated for Cd oxide fumes. The absorption of other Cd compounds may vary greatly, depending on the chemical species and the particle size. Of circulating Cd, >90% is bound to erythrocytes.

Cd is a cumulative element with a biological half-life of >10 years in man. It accumulates mainly in the kidney and in the liver, with ~50% of the body burden in these two organs. In the general population the concentration of Cd in the kidney increases progressively with age at least until age 50-60, and then tends to decline. Liver concentration does not show a clear de-

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crease in the elderly. Estimates of the mean body burden of nonoccupationally exposed adults range from 5 to 20 mg. The body burden of smokers is about twice that of nonsmokers. In tissues, Cd is bound mainly to metallothionein, whose production is stimulated by Cd exposure. Cd is excreted via the urine and to a smaller extent through the bile, the gastrointestinal tract, saliva, hair, nails, and breast milk.

In man, the three main targets after long-term Cd exposure are lung, bone, and kidney, but it is generally accepted that the kidney is the critical organ, i.e., the organ that exhibits the first adverse effects (1). High past industrial exposure may be associated with an increased risk of cancer (mainly in the lung), but confounding factors (e.g., concomitant exposure to arsenic) have not yet been adequately accounted for (2).

Biologic Markers of Exposure

It is possible to measure directly by neutron activation or x-ray fluorescence the amount of Cd that has accumulated in the liver and in the kidney. The technique, however, is not widely available. Indirect biologic indicators, such as Cd concentrations in blood, urine, feces, and hair, or metallothionein concentration in urine, have been proposed to assess either the current exposure or the amount of the metal accumulated in the body (internal dose). The significance of these markers can be briefly summarized as follows.

Cd in Blood

Blood Cd concentration is influenced by both the body burden and recent exposure, but several observations in the general population, in workers moderately exposed to Cd, and also experimental data suggest that Cd in blood mainly reflects the last few months of exposure. In newly exposed workers, the Cd concentration increases progressively for 4-6 months and then levels off at a value that is proportional to the average intensity of exposure (3). Reduction of exposure intensity is associated with a progressive decline of the Cd concentration in blood (half-time 2-3 months). However, in subjects who have been highly exposed in the past and have accumulated large amounts of Cd, the body burden may play a significant role in determining the concentration in blood (4).

For the general population, blood Cd is mainly influenced by the current exposure and less by the body burden, as shown by the very weak tendency of this parameter to increase with age (5). In nonoccupationally exposed adults who are nonsmokers, the Cd concentration in blood is generally <18 nmol/L ($n = 5$) (1, 6). Higher values (up to 44 nmol/L) have been found in smokers.